pantiIL-8.2, E. coli strain 294 mm	97056	February 10, 1995
p6G425chim2, E. coli strain 294 mm	97055	February 10, 1995
p6G4V11N35A.F(ab')$_2$	97890	February 20, 1997
E. coli strain 49D6(p6G4V11N35A.F(ab')$_2$)	98332	February 20, 1997
p6G425V11N35A.choSD	209552	December 16, 1997
clone#1933 aIL8.92 NB 28605/12	CRL-12444	December 11, 1997
clone#1934 aIL8.42 NB 28605/14	CRL-12445	December 11, 1997

REMARKS

Claims 1-7, 19-22, 26-29 and 31-36 were pending in this application. Claims 1, 5, 19, 21, 26, 28, 29 and 31-36 were rejected.

Objections

(1) Title

The title of the invention was objected by the Examiner for being "not descriptive." The title has been amended, as suggested by the Examiner, to be clearly indicative of the invention to which the claims are directed.

(2) Specification

The Applicant was requested by the Examiner to amend the address of the ATCC provided on page 207, at line 9 and page 241 at line 8 to reflect the current address for the American Type Culture Collection. The foregoing amendment complies with this requirement.

Rejections under 35 U.S.C. § 112, first paragraph

Claims 1, 5, 19, 21, 26, 28-29 and 31-36 were rejected under 35 U.S.C. § 112, first paragraph "as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention." The Examiner specifically noted that "the specification does not provide a sufficiently enabling description of the claimed invention," and further noted that "the specification does not appear to provide sufficient guidance as to how only a single PEG, as currently recited, may be covalent coupled to the recited Fab' fragment having two reactive cysteines."

Applicants respectfully traverse the rejection.

Example T of the present invention describes the modification of a Fab' antibody fragment with a single PEG molecule at the free cysteine at the carboxy terminal end of the hinge region. Example T further provides protocols for the protection of the free cysteine with 4',4'-dithiodipyridine (PDS) and subsequent deprotection with dithiothreitol (DTT). Accordingly, the Examiner's assertion that it would require undue experimentation to determine how to covalently couple a single PEG to the "interchain" cysteine seems to be clearly misplaced. A person skilled in the art would know how to protect the carboxy terminal cysteine before coupling a single PEG to the "interchain" cysteine, and subsequently deprotecting the carboxy terminal cysteine to produce the claimed PEG-derivative. Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Rejections under 35 U.S.C. § 102(e)

Claims 1, 5, 19, 21, 26, 28-29 and 31-36 were rejected under 35 U.S.C. § 102(e) "as being anticipated by U.S. Pat. No. 6,133,425 (of record)." Claims 1, 5, 19, 21, 26, 28-29 and 31-36 were further rejected under 35 U.S.C. 102(e) "as being anticipated by U.S. Pat. No. 6,025,158 (of record)." However, the Examiner noted that "this rejection under 35 U.S.C. 102(e) might be overcome...by showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention 'by another.'"

A Declaration under 37 C.F.R. § 1.132 of Leonard Presta and Steven Leong, inventors of the present application and U.S. Pat. Nos. 6,133,426 and 6,025,158, is submitted with the present Amendment and Response. The Declaration serves to show that any invention disclosed but not claimed in U.S. Pat. Nos. 6,133,426 and 6,025,158 was derived from the inventors of the present application and is thus, not considered to be an invention "by another."

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Obviousness-Type Double Patenting Rejections

(1) Claims 1, 5, 19, 21 and 31-35 were provisionally rejected "under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 13,

15-16, 18, 19, 21, 24, 26, 29, 32-37 of copending Application No. USSN 09/489,394." The Examiner noted that "although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the '394 application recite all the limitations recited in the instant claims, indicating that the limitations set forth in the instant claims were obvious embodiments of the invention claimed in USSN 09/489,394."

(2) Claims 1, 5, 19, 21, 26, 28-29 and 31-35 were provisionally rejected "under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 5, 8, 12-19, 21, 24-26 and 28-35 of copending Application No. USSN 09/726,258." The Examiner noted that "although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the U.S. 09/726,258 application recite all the limitations recited in the instant claims, indicating that the limitations set forth in the instant claims were obvious embodiments of the invention claimed in USSN 09/726,258."

Applicants respectfully disagree and traverse the rejections.

A proper basis for the judicially created doctrine of obviousness-type double patenting rejection exists only if any claim in the application define an invention that is merely an *obvious variation* of an invention claimed in the copending application.

Applicants point out that the scope of claims 1, 5, 19, 21 and 31-35, all of which are dependent on claim 1, of the instant application is different from the scope of claims 1, 5, 13, 15-16, 18, 19, 21, 24, 26, 29, and 32-37, all of which are dependent on claim 1, of co-pending Application No. 09/489,394. Further, the scope of claims 1, 5, 19, 21, 26, 28-29 and 31-35, all of which are dependent on claim 1, of the instant application is different from the scope of claims 1, 5, 8, 12-19, 21, 24-26 and 28-35, all of which are dependent on claim 1, of co-pending Application No. 09/726,258.

Independent claim 1 of the present application recites a conjugate consisting of a Fab' antibody fragment that is derivatized with a single polyethylene glycol (PEG). Specifically, the claims teach the attachment of PEG to a cysteine residue in one chain that would be in a disulfide bridge with a corresponding cysteine residue in the opposite chain if not for the substitution of the corresponding cysteine residue with another amino acid residue. Neither independent claim 1 of copending Application Nos. 09/489,394 nor 09/726,258 teach or suggest derivatizing a cysteine that is *ordinarily* in a disulfide bridge with a corresponding cysteine residue in the

opposite chain. Accordingly, the cited claims from the co-pending applications are similar but not identical in scope to the claims of the present application. Further, the claims pending in the present application, in light of the presence of language limiting the means of attachment of the PEG to the cysteine residue, are clearly more narrow than the cited claims of the co-pending applications. Applicants respectfully submit that the present claims *are* patentably distinct from the cited claims in the U.S. 09/489,394 and U.S. 09/726,258 applications. Thus, the obviousness-type double patenting rejections are believed to be improper and should be withdrawn.

Even if the Examiner considered restating this rejection relying on the judicially created doctrine of obviousness-type double patenting, it is believed that this would be the sole rejection remaining in the present case. Accordingly, the proper procedure would be to withdraw the rejection in the present application, and restate it in copending Application Nos. 09/489,394 and U.S. 09/726,258. Accordingly , the Examiner is respectfully requested to reconsider and withdraw the present rejection.

Applicants believe that all claims pending in this application are in *prima facie* condition of allowance, and an early action to that effect is respectfully solicited. Should the Examiner find that there are any further issues outstanding, she is invited to contact the undersigned attorney at the telephone number indicated below.

Although no fees are believed to be due at this time, please charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: _____ By: _____

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Version with markings to show changes made

In the Specification:

The title has been amended as follows:

--ANTIBODY FRAGMENT-POLYMER CONJUGATES [AND HUMANIZED ANTI-IL-8 MONOCLONAL ANTIBODIES]--

The paragraph beginning at page 206, line 1, has been amended as follows:

--Production of a $F(ab')_2$ version of the humanized anti-IL-8 6G4V11N35A Fab was accomplished by constructing a fusion protein with the yeast GCN4 leucine zipper. The expression plasmid p6G4V11N35A.$F(ab')_2$ was made by digesting the plasmid p6G425chim2.fab2 with the restriction enzymes bsaI and apaI to remove the DNA sequence encoding the 6G4.2.5 murine-human chimeric Fab and replacing it with a 2620bp bsaI-apaI fragment from pPh6G4.V11N35A. The plasmid p6G425chim2.fab2 is a derivative of pS1130 which encodes a fusion protein (the GCN4 leucine zipper fused to the heavy chain of anti-CD18) and the light chain of anti-CD18 antibody. The expression plasmid p6G4V11N35A.$F(ab')_2$ was deposited on February 20, 1996 with the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209[12301 Parklawn Drive, Rockville, MD], U.S.A. (ATCC) and assigned ATCC Accession No. 97890. A pepsin cleavage site in the hinge region of the antibody facilitates the removal of the leucine zipper leaving the two immunoglobin monomers joined by the cysteines that generate the interchain disulfide bonds. The DNA and protein sequence of the h6G4V11N35A.$F(ab')_2$ are depicted in Figs 35-37.--

The paragraph beginning at page 240, line 21, has been amended as follows:

--In the rabbit model of ear ischemia reperfusion injury, antibody was administered intravenously at a single dose (5 mg kg) at the time of reperfusion. In this model, ischemia reperfusion injury is characterized by tissue damage, edema and sometimes necrosis; all attributable in part to neutrophil-mediated damage. Monitoring of ear volume over time is a surrogate end-point for evaluating edema in the ear tissue. The resulting data (depicted in Fig. 71) showed that treatment with 20 kD linear PEG-, 30 kD linear PEG- and 40 kD branched PEG-conjugated Fab's effectively reduced ear swelling and edema at all time points of observation (days 1, 3 and 5). In fact, the efficacy of all three PEGylated Fab's was statistically

indistinguishible from that of the full length IgG murine anti-rabbit IL-8 monoclonal antibody 6G4.2.5 at all time points observed. These data support the efficacy of large effective size anti-IL-8 Fab'-PEG conjugates in ischemic reperfusion injury and specifically support the ability of 40 kD branched PEG-conjugated Fab' molecules to reach and act on disease effector targets in circulation and other tissues.

The following biological materials have been deposited with the American Type Culture Collection, 10801 University Boulevard, Manassas, VA 20110-2209[12301 Parklawn Drive, Rockville, MD], USA (ATCC):

Material	ATCC Accession No.	Deposit Date
hybridoma cell line 5.12.14	HB 11553	February 15, 1993
hybridoma cell line 6G4.2.5	HB 11722	September 28, 1994
pantiIL-8.2, E. coli strain 294 mm	97056	February 10, 1995
p6G425chim2, E. coli strain 294 mm	97055	February 10, 1995
p6G4V11N35A.F(ab')$_2$	97890	February 20, 1997
E. coli strain 49D6(p6G4V11N35A.F(ab')$_2$)	98332	February 20, 1997
p6G425V11N35A.choSD	209552	December 16, 1997
clone#1933 aIL8.92 NB 28605/12	CRL-12444	December 11, 1997
clone#1934 aIL8.42 NB 28605/14	CRL-12445	December 11, 1997